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Joana dos Santos Frasco

Prospective evaluation of limited joint mobility in type 1 Diabetes Mellitus: from adolescence to adulthood

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E sob a Coorientação de:
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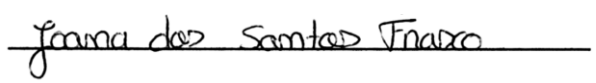

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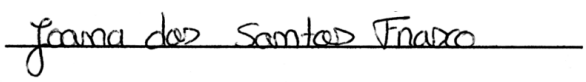

Dedicatória

Aos meus pais, ao meu irmão e a todos os meus familiares. Ao Diogo. A todos os meus amigos.

A ti, Esperança.

A ti, que nos dás força,
A ti, que nos impões simplicidade.
A ti, que nos acordas
e com o rosto sereno
nos ergues de manhã.
A ti, que nada pedes
a não ser um pouco de música
e nada exiges
e nos dás a tua própria ternura.
A ti, que diariamente nos acolhes
e nos trazes riso fresco
e nos dás uvas
e nos fazes cantar nas horas difíceis.
A ti, que ofereces água
a todos que passam
e mostras um caminho
aos poucos iluminados.
A ti, que com a tua dança,
o teu ritmo, o teu fogo
transformas as paisagens
e deixas ruas cor de ouro
e deixas árvores cor de linho.
A ti, que estás suspensa na noite
como uma lua branca,
e nos enches com a tua claridade
e nos dás esta grande confiança,
esta alegria imensa de crianças.
A ti esperança, eu dedico
agora e sempre
este poema.

João Rui de Sousa

Prospective evaluation of limited joint mobility in type 1 Diabetes Mellitus: from adolescence to adulthood

Limited joint mobility in type 1 diabetes

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OBJECTIVE: To study the longitudinal relationship of limited joint mobility (LJM) expression, severity and evolution with glycemic control and to determine its association with retinopathy and albuminuria in type 1 diabetic patients.

RESEARCH DESIGN AND METHODS: A total of 26 type 1 diabetic adolescents aged 13-18 years and with a disease duration ≥ 5 years were prospectively followed between 2007-2013 with repeated measurements of HbA_{1c} levels and assessments of retinopathy and albuminuria. Retrospective HbA_{1c} levels were also obtained. LJM was accessed twice, once in 2007 and again in 2013.

RESULTS: Overall prevalence of LJM was 85%. Prevalence of each LJM stage significantly changed between the two evaluations (p=0.049); 69% of the patients showed a regression/maintained their initial stage while 31% progressed to a severer one. Progression group had higher mean HbA_{1c} levels than the regression/no-evolution group (9.8 ± 1.3 vs 8.6 ± 1.2%, p=0.03). Patients with final stage ≥ 2 had higher mean HbA_{1c} than stage-0 (9.9 ± 0.9 vs 8.6 ± 0.7%, p=0.01) and than stage-1 patients (9.9 ± 0.9 vs 8.2 ± 0.9%, p=0.01). Both presence and evolution of LJM weren't significantly associated with retinopathy and albuminuria.

CONCLUSIONS: Severer stages and progression of LJM are associated with poorer glycemic control in adolescents and young adults with type 1 diabetes. Inclusion of LJM assessment in the follow-up routine should be considered, especially in these patients. Larger longitudinal studies with several evaluations of LJM are fundamental to evaluate more fully its clinical course and association with glycemic control and microvascular complications.

Type 1 Diabetes Mellitus is a chronic disease associated with significant morbidity not only due to the extensively known and studied micro and macrovascular complications but also due to its several rheumatic and musculoskeletal manifestations (1; 2). Among these manifestations the most frequent are those affecting the upper limb, specially the hands (2) and so the term "diabetic hand" has arisen, encompassing a range of conditions that affect the hands of diabetic patients including limited joint mobility (LJM) in first place but also Dupuytren's contracture, flexor tenosynovitis and others (3).

LJM is the first clinically apparent long-term complication of type 1 diabetes (4). It affects primarily the hands and is characterized by painless, non-inflammatory limitation of extension of the finger joints in association with thick and waxy skin, particularly on their dorsal surface. The onset of LJM is insidious; it usually begins in the fifth finger and then progresses radially with hands being symmetrically affected in most of the cases. The first and most frequently limited joints are the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints; gradually, it can start to affect metacarpophalangeal (MCP) joints and, in later stages, may extend beyond the hands to peripheral large joints of both upper and lower limbs as wrists, elbows, knees, ankle and inclusive to spine (5-9). The diagnosis of this condition is essentially clinical and can be made with the help of two clinical signs: the "prayer sign" and the "tabletop test" (5; 7; 10). Laboratory, imaging, and nail fold capillaroscopy findings are usually unremarkable or nonspecific (5; 8).

LJM was first reported as particularly associated with juvenile type 1 diabetes by Rosenbloom in 1974 (11) and it was only since then that larger studies on this topic started to be conducted, corroborating these findings (6; 8). The estimated prevalence of LJM among diabetic patients varies widely according to different authors, ranging from 8 to 58% in type 1 diabetes (2) but it's often suggested at between 30 and 40% by most studies (8). There is also significant evidence that the frequency of LJM increases with increasing diabetes duration (12-

14), with pre-pubertal onset of diabetes (15) and with puberty (16), being more common between the ages of 10 and 20 and rare before the age of 10 (2; 4). Moreover, no gender or racial differences have been found (8; 10).

The early recognition of this condition is important because there is some evidence that it is associated with poor glycemic control (13; 16; 17) and with diabetic microvascular complications (13; 14; 16; 18-20). However, most of the studies focused on these topics are cross-sectional, with only a few of them having a prospective design. Moreover, in most of the cases, results are conflicting and therefore many questions still with no conclusive answer. For instance, whether careful glycemic control can prevent the onset of LJM or improve/stabilize the LJM already established is unknown; similarly, the extent to which LJM serves as an early marker of ongoing retinopathy/nephropathy has not been conclusively determined (2; 8).

The current study aims to determine the longitudinal relationship of LJM presence and severity with glycemic control in type 1 diabetic patients and to understand the extent to which the evolution of LJM depends on glycemic control. It also pretends to evaluate the association of LJM with retinopathy and albuminuria.

RESEARCH DESIGN AND METHODS

We conducted a longitudinal prospective study with beginning in 2007 and ending in 2013, in a total of 6 years of follow-up.

Consecutive type 1 diabetic patients were recruited from the pediatric endocrinology outpatient consultation of Centro Hospitalar São João during over a one year period. Patients must had a documented date of diabetes diagnosis and should be followed in this hospital's consultation from soon after that time in order to have reliable retrospective data. Only patients aged between 13 and 18 and with a disease duration of 5 or more years were included. All the

other patients were excluded as well as those who had a history of hand injury, Dupuytren's contracture, flexor tenosynovitis or any other hand disorder that could misunderstood the evaluation of LMJ. With this criteria, we were able to recruit 46 patients into de study by 2007. However, due to hospital transfers or repeated absences to scheduled appointments, there were some subjects lost to follow-up which were excluded from the final sample. In the end, we counted with a total of 26 patients.

Informations about patient's age, duration of diabetes, age of diagnosis, HbA_{1c} levels, status of retinopathy and albuminuria were recorded for each patient in 2007 first evaluation. All retrospective information needed was obtained from medical files. During the follow-up time, patients visited the hospital every two to four months in the context of their routine outpatient follow-up and updated informations about HbA_{1c} levels, retinopathy and albuminuria status were also recorded.

Joint mobility was only accessed twice, once in 2007 and again in 2013. There were no retrospective informations about it for any of the patients. The observer was the same for all patients within the same year but different between the two evaluations. Nevertheless, the exactly same methods were used and last examiner was blinded to previous results. The "tabletop test" and "prayer sign" were performed subsequently to assess joint mobility. The "prayer sign" was positive if the patient was unable to completely approximate the palmar surface of the hands and fingers when asked to raise the hands in a praying position with the fingers fanned and wrists extended (5; 18; 21). The "tabletop test" was positive if the patient was unable to make contact of the entire palmar surface to a table when asked to flatten the palm of his hand with the fingers fanned against the table's surface (5; 8; 22). Metacarpophalageal joint contractures were detect by asking the patient to lift the palm from the table while keeping the fingers on it (15). When one or both of these maneuvers were positive, the examiner confirmed the limited mobility by attempting to extend the fingers

passively; there was a loss of passive extension if the range of extension was less than 180° at the PIP and DIP joints, less than 60° at the MCP joints and less than 70º at wrist (5; 7; 18). Joint mobility was staged from 0 to 3 based on the classification of Grgic et al. (22) - stage 0: entire palmer surface contacts with the table and there is no limitation; stage 1: only one finger of one or both hands is affected; stage 2: two or more fingers of each hand are affected; stage 3: all fingers of both hands plus some larger joint (wrist) are affected. Comparing the first evaluation's stage with the last one, patients were included in one of three groups: regression (if initial stage > last stage), no-evolution (if initial stage = last stage) and progression (if initial stage < last stage). Overall, patients were included in "with LJM" group if they presented limitation of joint mobility in any of the two evaluations; the remainder were included in "without LJM" group.

Glycemic control was measured by HbA_{1c} levels. All its retrospective determinations from soon after diagnosis of diabetes were recorded. During follow-up time, HbA_{1c} levels were determined from blood samples taken during outpatient visits. At least two measurements were recorded per year per patient.

Retinopathy status was determined annually by a trained ophthalmologist and considered to be present if it was diagnosed in any of its forms (non-proliferative or proliferative).

Albuminuria status was determined by measurement of the albumin excretion and albumin/creatinine ratio (ACR) in random spot urine collections. A patient was considered to have developed increased urinary albumin excretion (Albuminuria+) only if more than two consecutive specimens collected were abnormal (ACR ≥30 mg/g creatinine) and were then confirmed by an abnormal 24h urine analyses (≥30 mg/24h). Both persistent albuminuria (at levels 30–299 mg/24h and levels >300 mg/24h) and transient albuminuria were included in the same category (23). Isolated abnormal ACR and 24h albumin excretion <30 mg/24 h were considered normal.

Ethical approval was obtained from ethical committee of the Centro Hospitalar São João. Adolescents were asked to assent before entering the study and oral informed consent was obtained from the parents prior to their inclusion. Written consent was also obtained from patients in the second LJM evaluation in 2013.

Statistical analyses

All continuous variables were accessed for their normality using Shapiro-Wilk normality test. Normally distributed data are expressed as means ± SE; otherwise the median (range) is used. Differences in normal continuous variables between groups were analyzed using the parametric tests Independent Samples T Test, Paired-Samples T Test or One-way ANOVA with Bonferroni correction for post-hoc testes when necessary. When parametric tests' assumptions were not verified or variables didn't follow a normal distribution, comparison between groups were done using non-parametric Mann Whitney U Test. Chi-square testing allowed comparisons between categorical variables. In some analysis, data from groups with LJM stages 2 and 3 as well as from regression and no-evolution group were combined. IBM SPSS Statistics version 21 was used for analysis. A p-value <0.05 was considered significant.

RESULTS

Demographic and clinical characteristics of the sample

A total of 26 patients (14 males and 12 females) with type 1 diabetes meeting the inclusion and follow-up criteria were included in the statistical analyses. Characteristics of the sample at the beginning of the study are shown in Table 1. The mean age of the patients was 14.9 ± 1.6 years with a median duration of diabetes of 7.5 years (range 5-14). In terms of clinical characteristics, the mean HbA_{1c} of the sample was 9.3 ± 1.4% (78 ± 15.3 mmol/mol); none of the patients had documented retinopathy at the time and just 2 had evidence of

albuminuria. All patients were followed during the 6-years period from 2007 to 2013. By the end of the study, all patients had already reached adulthood; the mean HbA_{1c} was 9.1 ± 1.1% (76 ± 12.0 mmol/mol), retinopathy was present in 39% (n=10) of the patients and albuminuria in 27% (n=7).

LJM prevalence, staging and evolution

The prevalence of LJM (stage>0) in 2007 was 58% (n=15) compared with 70% (n=19) in 2013. The distribution of LJM stages significantly changed between the two evaluations: stage-0 prevalence decreased from 42 to 27%; stage-1 increased from 23 to 27%; stage-2 increased from 19 to 35% and stage-3 decreased from 15 to 12% (p=0.049). Patients with the same initial stage showed different evolutions during the follow-up time, being able to present a less or a more severe final stage than the initial one (Figure 1). In a global view, 69% of patients showed a regression or maintained the initial stage while 31% progressed to a more severe one. The characteristics of each evolution group are listed in Table 2. The median diabetes duration, age as well as the gender distribution wasn't statistically different between the two groups.

By the end of the study, patients with LJM represented 85% (n=22) of the sample and those without LJM represented the remaining 15% (Table 3). As for the evolution groups, no differences in diabetes duration, age and gender distribution were observed between patients with and without LJM.

Relation of LJM presence, evolution and severity to glycemic control

Mean HbA_{1c} levels during the follow-up period were significantly higher in those patients of the progression group compared to those of the regression/no-evolution group (9.8 ± 1.3 vs 8.6 ± 1.2%, p=0.03) (84 ± 14.2 vs 70 ± 13.1 mmol/mol). Similar findings were observed within the groups of patients with the same initial stage: for a given initial stage, patients who

regressed to a less severe stage had lower mean HbA_{1c} levels during the follow-up than those who maintained or progressed to a severer one; similarly, patients who maintained the same stage had lower levels than those who progressed (data not shown). However, these differences were not significant for any of the four initial stages. Using the mean of all HbA_{1c} values recorded until 2013 instead of using those recorded only during the follow-up period, similar comparisons reached significance and revealed overlapping results: HbA_{1c} levels were significantly higher in patients initially 0-staged that progressed to stage-1/stage-2 comparing with those who didn't (10.1 ± 1.0 vs 8.7 ± 0.7%, p=0.04) (87 ± 10.9 vs 72 ± 7.7 mmol/mol) and in patients initially 2-staged who remained in that stage compared with those who regressed to a less severe stage (9.3 ± 0.3 vs 8.0 ± 0.3%, p=0.01) (78 ± 3.3 vs 64 ± 3.3 mmol/mol). These differences were also observed for initial stage-3 group but statistical conclusions were not possible due to small numbers.

Comparing the mean HbA_{1c} levels until 2007 with the mean HbA_{1c} levels during the follow-up period, in the regression/no-evolution group these values decreased from 9.1 ± 1.5 to 8.6 ± 1.2% (76 ± 16.4 to 70 ± 13.1 mmol/mol) and in the progression group increased from 9.5 ± 1.3 to 9.8 ± 1.2% (80 ± 14.2 to 84 ± 13.1 mmol/mol); however, these differences were not significant in any of the groups. Doing the same comparison between the two periods but taking into account the initial stage, patients who progressed from stage-0 to stage-1 or to stage-2 had higher mean HbA_{1c} values during the follow-up period compared to before (9.1 ± 0.1 vs 8.4 ± 0.4%; 10.5 ± 1.3% vs 10.2 ± 1.0%, respectively) (76 ± 1.1 vs 68 ± 4.4 mmol/mol; 91 ± 14.2 vs 88 ± 10.9 mmol/mol) and patients who regressed from stage-1 to stage-0 had lower values during follow-up (7.8 ± 0.2 vs 9.1 ± 1.6%) (62 ± 2.2 vs 76 ± 17.5 mmol/mol) although differences didn't reach significance; comparisons for other evolution pares were not possible due to the small numbers.

By the end of the study, mean HbA_{1c} levels were higher in patients with LJM compared to those without LJM but the difference was not significant. No differences were found in HbA_{1c} levels between males or females with or without LJM. Taking into account the severity of the final stage, in patients with final stage ≥ 2 the mean HbA_{1c} for all disease duration was higher than in stage-0 patients (9.9 ± 0.9 vs 8.6 ± 0.7%, p=0.01) (85 ± 9.8 vs 70 ±7.7 mmol/mol) and than in stage-1 patients (9.9 ± 0.9% vs 8.2 ±0.9%, p=0.01) (85 ± 9.8 vs 66 ± 9.8 mmol/mol).

Relation of LJM to retinopathy and albuminuria

There was no difference in the prevalence of retinopathy and albuminuria between patients with and without LJM. This proportion was also not different between the progression and regression/no-evolution groups. The relative risk for the presence of microvascular complications showed no significant risk for patients with LJM: RR of retinopathy was 1.6 (95% CI: 0.3-9.6) and RR of albuminuria 1.1 (95% CI: 0.2-6.8).

CONCLUSIONS

Musculoskeletal manifestations associated with type 1 diabetes are frequently under-recognized and overlooked in spite of being quite common and responsible for substantial morbidity (5). LJM is usually asymptomatic and non-disabling but later in the course of the condition it can lead to fixed flexion contractures of the small hand joints, to decreased grip strength and to an impaired dexterity and ability to perform fine hand movements (7; 8; 10). However, the importance of LJM is not just related with the condition itself but also with its presumable association with glycemic control and microvascular complications. LJM pathogenesis can be postulated as the explanation for these associations. There is evidence that persistent hyperglycemia leads to non-enzymatic glycosylation of collagen resulting in accumulation of abnormal cross-linked collagens resistant to degradation that are responsible

for abnormal stiffening of the peri-articular soft tissue; these changes also lead to microvascular abnormalities and vascular ischemia, characteristic changes of diabetic microangiopathy (6; 8; 10). This abnormal glycosylation may be reversible early in the course of the disease or decreased with improved glycemic control but become irreversible later, once cumulative damage to collagen has occurred (24).

Overall prevalence of LJM in our study (85%) was a quite higher than that founded by other reports. We attribute this this fact to our definition of LJM and to some of our selection criteria once puberty, age and diabetes duration are associated with higher prevalence of LJM (12; 16). The current study detected any differences between genders. However, unlike the most of the studies, it didn't also detect a significant increased prevalence of LJM with increasing age and diabetes duration, maybe due to the small range of age and diabetes duration of our sample.

Most of the cross-sectional studies have shown no association between LJM and the presence of higher HbA_{1c} levels (12; 25-27) but longitudinal studies have confirmed this relation, indicating that the lack of association maybe was due to the use of only a single HbA_{1c} value (13; 16; 17; 28). Moreover, two studies in type 1 diabetic patients have shown a decrease in LJM prevalence during a two decades interval, what was attributed to more intensive treatment strategies and improved glycemic control (12; 29). In our study, mean HbA_{1c} levels were higher in patients with LJM but, in contrast to the referred longitudinal studies, this result wasn't significant probably due to the small number of our sample. However, when different stages of severity were considered, poor glycemic control was significantly associated with the most severe stages of LJM (stages $\geq$ 2) while other patients had a proved better glycemic control. These findings are in agreement with other studies where LJM severity was considered (13; 16). Thus, and considering the reduction in the number of cases with moderate to severe joint limitation also found along with the decrease in LJM prevalence (12; 29), we can

hypothesize that differentiation between different stages of LJM severity might be as or more important than the presence/absence of LJM when considering the role of glycemic control.

Faced with the observation that different patients had a different evolution of their joint mobility during the follow-up period, we hypothesized that differences in joint mobility evolution could be related to differences in glycemic control. Few studies analyze this evolution issue and its relation with other parameters. One study concluded that higher HbA_{1c} concentrations are predictive for progression of LJM (28). The possibility of regression/improvement of LJM is also rarely addressed. Only some case reports have shown an improvement and even a complete resolution of LJM along with a decrease in HbA_{1c} values (8; 30). In our study, we had similar findings: patients with progression of their initial limitation had poorer glycemic control during the follow-up period than patients whose limitation has improved or at least didn't progressed; these findings appeared to be independent of the initial stage's severity. However, the extent to which an improvement in individual glycemic control would lead to an improvement of LJM or at least could avoid its progression and, on the other hand, a worsening would be responsible for the progression couldn't be clarified: patients who progressed to a severer stage had higher HbA_{1c} levels in the follow-up period compared with before in the same way that patients who regressed or maintained the same limitation had lower HbA_{1c} levels but differences between the two time periods weren't significant so we can't prove these associations. One explanation for this could be that the degree of glycemic control is more important than its improvement/worsening in LJM evolution; still, we believe that a change in glycemic control can influence LJM evolution.

We didn't detect any significant differences in the prevalence of retinopathy or albuminuria between patients with or without LJM and neither between the different evolution groups. Moreover, there was no significant risk for the presence of these complications in patients with LJM. In spite of our results, several studies have shown that LJM is significantly

associated with both retinopathy and nephropathy in type 1 diabetes (4; 18-20). In a study, the presence of LJM conferred a more than 3-fold increased risk of having microvascular complications (18); a prospective study also concluded that the onset of LJM is associated with a 1.9-fold greater risk of developing microalbuminuria (16). Based on these findings, some authors consider that LJM may be an indicator of the risk of developing these complications while others suggest that in spite of the association, LJM cannot be used as a predictor (25).

We are aware of the several limitations of our study. The small size of our final sample is an important limitation since it may not only limit generalizations of our results but also contribute to the lack of significance of some comparisons. The strict selection criteria and the fact that our sample belongs to a specific clinic population could introduce some selection bias and also limit generalizations but, on the other hand, reduced the variability of the sample and the influence of diabetes duration, age and puberty. A further potential bias is that a different observer undertook 2013 assessments of LJM what could introduce some inter-observer variability. This variability could also account for the observed possibility of LJM evolution. To attenuate this possible bias, the same evaluation methods were carefully followed by both examiners, the abovementioned LJM definition was used and regression and no-evolution groups were grouped for statistical analyzes. In spite of these limitations, we would like to highlight the importance of having the same single observer for all the assessments performed within the same year. Furthermore, this is one of the few studies which describes the longitudinal evolution of LJM and its association with glycemic control.

In summary, severer stages and progression of hand joint limitation are associated with poorer glycemic control in type 1 diabetic adolescents and young adults. Current literature supports that microvascular complications are also associated to chronic hyperglycemia (1) and to LJM (4; 18-20), so we can suppose that a better glycemic control would prevent and delay both LJM and microvascular complications and that LJM's assessment could alert the

physician to the likely presence of retinopathy and nephropathy (8). This evaluation would not, however, substitute their annual screening (16) but could maybe justify doing it sooner than the 5-years of diabetes duration actually defined by the current guidelines (23), especially in pubertal/young adults patients with severe limitation. LJM assessment can be easily done without time-consuming examinations and so should be a part of the follow-up routine of type 1 diabetic patients (8). Nevertheless, larger longitudinal studies with repeated evaluations of LJM using a standardized method are fundamental to evaluate its clinical course, evolution and relation with microvascular complications more fully.

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Author Contributions

J.F. collected data, researched on literature, performed the statistical analysis and wrote the manuscript. M.S. collected data, researched on literature and reviewed/edited the manuscript. P.F. reviewed/edited the manuscript.

Conflict of Interest

The authors declare no conflict of interest of any type, inclusive institutional or financial.

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TABLES

Table 1 - Demographic and clinical characteristics of the sample at the beginning of the study (2007)

Sample size (n)	26
Gender (M/F)	14/12
Age (years)	14.9 ± 1.6
Age of diabetes diagnosis (years)	7.1 ± 3.1
Duration of diabetes (years)	7.5 (5-14)
HbA_{1c} (%)*	9.3 ± 1.4
HbA_{1c} (mmol/mol)	78 ± 14.2
Patients with retinopathy (n)	0
Patients with albuminuria (n)	2

Data are expressed as means (SD) or median (range) unless stated otherwise. * Mean of all values recorded on patient's medical files until 2007

Table 2 - Characteristics of Limited Joint Mobility evolution groups

	Regression/No-evolution	**Progression**	**p-value**
Frequency (n/%)	18 (69%)	8 (31%)	
Gender (M/F)	9/9	5/3	0.7
Duration of diabetes (years)	13.5 (11-20)	13.0 (11-18)	0.8
HbA_{1c} (%)*	8.6 (±1.2)	9.8 (±1.3)	0.03
HbA_{1c} (mmol/mol)	70 ± 13.1	84 (±14.2)	
Retinopathy (n/%) †	6 (33.3%)	4 (50%)	0.7
Albuminuria (n/%) †	2 (11.1%)	3 (37.5%)	0.3

Data are expressed as means (SD) or median (range) for the total duration of follow-up. * Mean of all values recorded during the 6-years follow-up period. † New cases during the follow-up time.

Table 3 – Characteristics of the sample comparing all subjects with and without Limited Joint Mobility

	With LJM	**Without LJM**	**p-value**
Frequency (n/%)	22 (85%)	4 (15%)	
Gender (M/F)	12/10	2/2	1.0
Duration of diabetes (years)	12.5 (11-18)	17 (11-20)	0.1
HbA_{1c} (%)*	9.2 (±1.2)	8.7 (±0.7)	0.4
HbA_{1c} (mmol/mol)			
Retinopathy (n/%) †	9 (41%)	1 (25%)	1.0
Albuminuria (n/%) †	6 (27%)	1 (25%)	1.0

Data are expressed as means (SD) or median (range) for the total duration of the disease. * Mean of all values recorded until 2013. † Total of cases for the total duration of the disease.

FIGURES

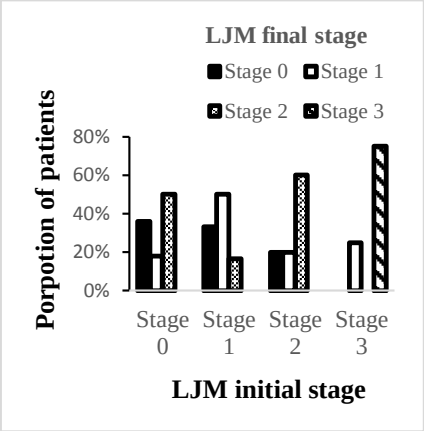

Figure 1 Evolution of LMJ during the follow-up time for each initial stage.

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ANEXOS

Anexo 1

Diabetes Care Instructions for Authors

Last updated on November 19, 2013.

Beginning with manuscripts submitted after Jan. 1, 2013, *Diabetes Care* requires authors to report HbA1c levels in both traditional, DCCT-derived units (as %) and SI, IFCC-recommended units (as mmol/mol). Authors should use the NGSP converter for HbA1c, available at http://www.ngsp.org/convert1.asp, to calculate HbA1c values as both % and mmol/mol. (Please note the additional link available for converting standard deviations.) Values should first be reported as %, followed by the mmol/mol equivalent in parentheses.

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